High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial

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Abstract: BACKGROUND: High-dose methotrexate is the standard of care for patients with newly diagnosed primary CNS lymphoma. The role of whole brain radiotherapy is controversial because delayed neurotoxicity limits its acceptance as a standard of care. We aimed to investigate whether first-line chemotherapy based on high-dose methotrexate was non-inferior to the same chemotherapy regimen followed by whole brain radiotherapy for overall survival. METHODS: Immunocompetent patients with newly diagnosed primary CNS lymphoma were enrolled from 75 centres and treated between May, 2000, and May, 2009. Patients were allocated by computer-generated block randomisation to receive first-line chemotherapy based on high-dose methotrexate with or without subsequent whole brain radiotherapy, with stratification by age (<60 vs 60 years) and institution (Berlin vs Tübingen vs all other sites). The biostatistics centre assigned patients to treatment groups and informed local centres by fax; physicians and patients were not masked to treatment group after assignment. Patients enrolled between May, 2000, and August, 2006, received high-dose methotrexate (4 g/m(2)) on day 1 of six 14-day cycles; thereafter, patients received high-dose methotrexate plus ifosfamide (1 · 5 g/m(2)) on days 3-5 of six 14-day cycles. In those assigned to receive first-line chemotherapy followed by radiotherapy, whole brain radiotherapy was given to a total dose of 45 Gy, in 30 fractions of 1 · 5 Gy given daily on weekdays. Patients allocated to first-line chemotherapy without whole brain radiotherapy who had not achieved complete response were given high-dose cytarabine. The primary endpoint was overall survival, and analysis was per protocol. Our hypothesis was that the omission of whole brain radiotherapy does not compromise overall survival, with a non-inferiority margin of 0 · 9. This trial is registered with ClinicalTrials.gov, number NCT00153530. FINDINGS: 551 patients (median age 63 years, IQR 55-69) were enrolled and randomised, of whom 318 were treated per protocol. In the per-protocol population, median overall survival was 32 · 4 months (95% CI 25 · 8-39 · 0) in patients receiving whole brain radiotherapy (n=154), and 37 · 1 months (27 · 5-46 · 7) in those not receiving whole brain radiotherapy (n=164), hazard ratio 1 · 06 (95% CI 0 · 80-1 · 40; p=0 · 71). Thus our primary hypothesis was not proven. Median progression-free survival was 18 · 3 months (95% CI 11 · 6-25 · 0) in patients receiving whole brain radiotherapy, and 11 · 9 months (7 · 3-16 · 5; p=0 · 14) in those not receiving whole brain radiotherapy. Treatment-related neurotoxicity in patients with sustained complete response was more common in patients receiving whole brain radiotherapy (22/45, 49% by clinical assessment; 35/49, 71% by neuroradiology) than in those who did not (9/34, 26%; 16/35, 46%). INTERPRETATION: No significant difference in overall survival was recorded when whole brain radiotherapy was omitted from first-line chemotherapy in patients with newly diagnosed primary CNS lymphoma, but our primary hypothesis was not proven. The progression-free survival benefit afforded by whole brain radiotherapy has to be weighed against the increased risk of neurotoxicity in long-term survivors.

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G-PCNSL-SG-1 randomised phase III trial of high-dose methotrexate with or without whole brain radiotherapy for primary central nervous system lymphoma

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Abstract

Background: High-dose methotrexate (HDMTX) is considered standard of care for patients with newly diagnosed primary central nervous system lymphoma (PCNSL). The role of whole brain radiotherapy (WBRT) has remained controversial: delayed neurotoxicity limits its acceptance as a standard of care. The aim of the G-PCNSL-SG-1 trial was to test the hypothesis that the omission of WBRT from first-line treatment based on HDMTX does not compromise overall survival (OS).

Methods: The G-PCNSL-SG-1 trial (www.clinicaltrials.gov NCT00153530) randomised (fax randomisation, based on computer-generated random list) immunocompetent patients with newly diagnosed PCNSL to chemotherapy followed by WBRT or chemotherapy alone. Patients were stratified according to age, < 60 *versus* ≥ 60 years, and institution (Berlin *versus* Tübingen *versus* all other sites). All patients were to receive 6 cycles HDMTX from 1999-2007 and HDMTX plus ifosfamide thereafter. Patients achieving a complete response (CR) received consolidating WBRT (45 Gy, 1.5 Gy fractions) (arm A1) or no further treatment (A2). Patients without CR received WBRT (B1) or HD-cytarabine (HD-Ara-C) (B2). The primary endpoint was overall survival (OS). We hypothesized that the omission of WBRT from first-line treatment does not compromise OS, using a non-inferiority design with a margin of 0.9. The per protocol population was used in the primary analysis.

Findings: 551 patients (median age 63 years) entered the study; of 526 who fulfilled the eligibility criteria, 66 died during HDMTX-based chemotherapy, 49 dropped out, and 411 entered the post-HDMTX phase; 318 were treated per protocol (PP

population). For this PP population, median OS was 32.4 months (95% CI 25.8-39) in the chemotherapy+WBRT arms (A1+B1, n=154) and 37.1 months (95% CI 27.4-46.7) in the chemotherapy alone arms (A2+B2, n=164) (p=0.7, HR 1.06, 95%CI 0.8-1.4). Thus the primary hypothesis was not proven. Median progression-free survival (PFS) was 18.3 (95% CI 11.6-25) and 11.9 months (95% CI 7.3-16.5, p=0.13). Treatment-related neurotoxicity in patients with a sustained CR was more common in the WBRT arm (22/45 = 48.9% by clinical assessment, 35/49 = 71.4% by neuroradiology) than in the chemotherapy alone arm (9/34 = 26.5% by clinical assessment, 16/35 = 45.7% by neuroradiology).

Interpretation: No significant difference in OS was found when WBRT was omitted from primary therapy in patients with newly diagnosed PCNSL. The PFS benefit afforded by WBRT has to be weighed against the probably increased risk of neurotoxicity in long-term survivors.

Funding: German Cancer Aid

Key words: primary central nervous system lymphoma, chemotherapy, whole brain radiotherapy, high-dose methotrexate, neurotoxicity

Introduction

PCNSL is a rare brain tumor with an annual incidence of 0.5/100,000 and a median age at diagnosis of 60-65 years (www.cbtrus.org). The incidence of PCNSL is supposed to be rising in immunocompetent individuals whereas it seems to be decreasing in HIV-positive patients. The median survival is in the range of 10-20 months. Survival at 5 years is below 20-30%.[1-6]

Standards of care have not been well defined yet. Surgical measures beyond a stereotactic biopsy to confirm the diagnosis are not recommended. WBRT induces complete remissions (CR) defined by neuroimaging in up to 60% of the patients, but their durations are usually short, and the median survival is in the range of only 12-18 months.[7] HDMTX administered at doses above 3.5 g/m^2 in 2-3 weeks intervals is the most active drug. The combination of HDMTX-based chemotherapy and WBRT, with or without intrathecal chemotherapy, produced both high response rates and extended survival up to 30-60 months in phase II studies,[8-11] but was associated with intolerable long-term neurotoxicity especially in the elderly.[12-13] Accordingly, various strategies maintaining treatment efficacy, but reducing toxicity, were explored, including the use of HDMTX alone.[14-16] However, the German NOA-03 trial did not confirm adequate response rates and survival times with HDMTX alone as the first-line treatment for PCNSL.[17-18] The response rate increased when HD-Ara-C was added to HDMTX as part of the first-line chemotherapy.[19] The role of WBRT added to HDMTX in the primary treatment of PCNSL has been identified as the most important question to address.[20] Accordingly, the G-PCNSL-SG already in 1999 designed a randomised trial (www.clinicaltrials.gov NCT00153530) to test the

hypothesis that primary HDMTX-based chemotherapy alone was not inferior to primary chemotherapy followed by WBRT for patients with newly diagnosed PCNSL (Figure 1).

Patients and Methods

Study design

The inclusion criteria were: PCNSL confirmed by histology or by cytology or immunocytochemistry from the cerebrospinal fluid (CSF), no prior cytostatic treatment, no evidence of extra-CNS involvement, written informed consent, age >18 years, life expectancy > 2 months, neutrophil count >1500/μl, platelets >100 000/μl, normal total bilirubin, transaminases < 3x the normal value and a creatinine clearance >50 ml/min. Major exclusion criteria were: concomitant immunosuppression including positive HIV serology, active infection, a Karnofsky performance score (KPS) < 50% for reasons not related to PCNSL and <30% for PCNSL-related reasons, concomitant malignancy, pregnancy, breast feeding, no effective contraception in women with child-bearing potential, and treatment with non-steroidal anti-inflammatory drugs, sulfonamides or penicillins within 1 week prior to HDMTX.

Staging included physical examination, mini-mental status examination (MMSE), biochemical serum profile, HIV, hepatitis B and C serological assessment, CT scans of chest and abdomen, brain MRI (CT when MRI was not available or possible), bone marrow biopsy, ophthalmological assessment, and CSF examination. Central

pathology review was recommended but not mandatory for enrolment. The patients were stratified according to age, < 60 *versus* ≥ 60 years, and institution (Berlin *versus* Tübingen *versus* all other sites).

Randomisation and masking

The patients were block-randomised using a randomisation list generated in the biostatistical center using a self-written computer program. New patients were announced by the local investigators via Fax. In this fax the local investigators documented demographic data necessary for stratification and confirmed informed consent. A reply fax disclosed the study arm, i.e., whether chemotherapy was to be followed by WBRT (A1, B1) or chemotherapy alone (A2, B2) (Figure 1). Treatment was not blinded (neither treating physicians, nor patients, nor evaluating physicians) as sham radiotherapy was not feasible and evaluating physicians were the same as treating physicians.

Study treatment

After randomisation, all patients were to receive 6 cycles HDMTX (4 g/m^2 as a 4 h i.v. infusion D1, biweekly) from 1999-2007 and HDMTX plus ifosfamide (1.5 g/m^2 as a 3 h i.v. infusion D3-5, biweekly) thereafter. This protocol amendment was a result of a continuous analysis of response to primary chemotherapy and reflected the increasing awareness of study sites that HDMTX alone might be an insufficient primary chemotherapy for PCNSL. HDMTX dose was adjusted to creatinine clearance. Dexamethasone, 3 x 8 mg, D1-10, was given to all patients in cycle 1. Supportive therapy included intensive i.v. hydration with urine alkalinization,

leucovorin 25 mg i.v. every 6 h starting 24 h after start of HDMTX and mesna 400 mg i.v., given before as well as 4 and 8 h after ifosfamide. Granulocyte colony-stimulating factor was not routinely given.

Response was evaluated by MRI or CT as well as CSF evaluation and slit-lamp examination in patients with CSF or ocular involvement. CR was defined as a complete resolution of contrast-enhancing lesions on MRI or CT and, in the case of initial CSF or ocular involvement, a disappearance of lymphoma cells from these sites. Central neuroradiology review after HDMTX-based chemotherapy was recommended.

HDMTX was given for 6 cycles even if patients achieved a CR earlier. Patients achieving CR received consolidating WBRT with 45 Gy in 1.5 Gy fractions (arm A1) or no further treatment (A2). Patients without CR received WBRT (45 Gy, 1.5 Gy fractions) (B1) or HD-Ara-C (2 x 3 g/m^2/day as a 3 h i.v. infusion D1-2 three-weekly) (B2), which then was assumed the second most active drug in PCNSL.[21] Stopping rules were: the upper 95% confidence limit for CR < 50% or grade 4 toxicity, hematotoxicity and alopecia excluded, in more than 10% of patients in at least one study arm.

After the end of study treatment, patients were observed longitudinally with MRI or CT, neurologic examination and additional examinations on clinical suspicion every 3 months for the first year, every 4 months in the second year, every 6 months in the third year and yearly thereafter. Treatment-related neurotoxicity was defined as progressive neurologic or cognitive impairment as documented in serial clinical examinations in the absence of recurrent lymphoma.

The primary endpoint was OS. Secondary endpoints were: CR rate with HDMTX-based chemotherapy, WBRT or HD-Ara-C, PFS, toxicity assessed by WHO classification 1996, and delayed neurotoxicity evaluated by clinical examination and white matter changes or brain atrophy on MRI or CT. Sequential MMSE data were planned to be collected, but were not obtained as scheduled in the majority of the patients.

The study protocol (http://www.neuroonkologie.de/index.php?id=58) was approved by the local institutional review boards or ethics committees. All participants gave written informed consent. The study was designed by E.T. and M.W., the founding chairmen of the G-PCNSL-SG. Study conduction and data assembly were coordinated by A.K.. The statistical design was developed by U.M. and P.M.. The statistical analysis was performed by P.M.. The manuscript was written by M.W., A.K., P.M. and E.T.. Preliminary data have been reported for HLA associations in 82,[22] treatment tolerability in the elderly in 154,[23] relapse patterns in 227,[24] CSF findings in 116,[25] and incidence of leptomeningeal dissemination in 282 patients.[26]

Statistical considerations

The goal of the trial was to demonstrate that the omission of WBRT from first-line treatment does not compromise OS as the primary endpoint. The CR rate on HDMTX was assumed to be 40%. A non-inferiority design was chosen with a margin of 0.9. Omission of WBRT was defined as non-inferior to WBRT if the lower two-sided 95% confidence limit of the hazard ratio (HR) of WBRT *versus* no WBRT was not below 0.9. The study was designed to have 60% power to prove non-inferiority of omission of WBRT in case of a HR of 1.2 of WBRT *versus* no WBRT. The sample

size required to detect this difference was 151 patients per group. Endpoints were measured from the time of randomisation. OS was measured until death, PFS until first progression or death. The total number of patients in the primary population (per protocol) was 318 (164 no WBRT *versus* 154 WBRT). We stopped recruitment with patient 318 because of the lag from recruitment to the assessment of the PP status. Chi-square tests were used to compare proportions. Mann–Whitney tests were used to compare quantitative and ordinal variables. Univariate analyses of survival were carried out by the Kaplan–Meier method. The evaluation of differences was performed with the log-rank test. The Cox proportional-hazards model was used to calculate HR and 95% confidence intervals. In addition, analyses were adjusted for potential prognostic factors regardless of differences between study arms. Data from patients who died without documented PD were defined as events in the PFS analysis. A two-sided p value of less than or equal to 0.05 was considered to indicate statistical significance. The analyses were carried out using PASW statisticals software release 18 (former SPSS).

Registration number

www.clinicaltrials.gov NCT00153530

Role of the funding source

The trial was reviewed by the German Cancer Aid, obtained the Certificate of Quality (*Gütesiegel A*), and was subsequently provided partial funding. The German Cancer Aid was not involved in the design of the trial or data collection or data interpretation. The funding source had no access to the data. ET, AK, PM and MW had full access

to the data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Patient characteristics and disposition

From 1999-2009, 551 patients (median age: 63 years) entered the study in 75 centers. Fourteen patients did not receive study treatment: 12 because they did not meet inclusion criteria (another histologic diagnosis, severe systemic infection or pulmonary embolism before chemotherapy, proof of systemic lymphoma manifestations) and 2 because they refused to participate. Eleven patients were excluded during initial HDMTX-based chemotherapy: 5 because of appearance of exclusion criteria (4 with lymphoma in the bone marrow and 1 with psychosis) and 6 for consent withdrawal. Of the remaining 526 patients, 66 patients died during HDMTX-based chemotherapy (see below), 27 dropped out for patient`s or physician`s decision, and 22 did not receive a response evaluation. Thus, 411 patients entered the post-HDMTX phase with a known response status and represent the intention-to-treat (ITT) population. Of these, 318 patients were treated as randomised and represent the per protocol (PP) population whereas 49 did not receive WBRT although randomised into arms A1/B1 and 44 without CR did not receive HD-Ara-C after HDMTX-based chemotherapy although randomised into arm B2 (Figure 2). During follow-up, 37 of 203 patients allocated to WBRT received salvage chemotherapy, 13 salvage radiotherapy, and 12 both. The 25 patients

treated with salvage radiotherapy had not received WBRT as randomised and were thus not irradiated twice. Of 208 patients allocated to no WBRT, 41 had salvage radiotherapy, 23 salvage chemotherapy, and 33 both (for details, see Web-Table 1, Webappendix).

Patient characteristics for the PP and the ITT-minus-PP populations are summarized in Table 1. There were no substantial differences for any parameter between the ITT and PP populations (data not shown), and, within the PP population, no difference for any parameter between arms A1/A2 and B1/B2 (data not shown). Patients in the WBRT arm within the PP population were 1.9 years older than patients in the non-WBRT arm. Ocular involvement was noted in less than 3% of the patients and thus less frequently than observed in other studies[19] whereas the rate of partial or complete resections was high, with almost 30%, possibly reflecting the participation of many primary care centers with limited experience in the management of PCNSL. Central pathology review was performed in 272 patients, and yielded the diagnoses compiled in Web-Table 2 (Webappendix). Given the non-inferiority design of the G-PCNSL-SG-1 trial, an analysis of the PP population is most conservative, therefore, all data reported below concern the PP population if not stated otherwise.

Acute toxicity

Of 526 patients, 66 (12.5%) died during HDMTX-based chemotherapy The causes of death were acute toxicity in 28 (5.3%), lymphoma progression in 24 (4.6%) and other reasons in 14 (2.7%) patients (pulmonary embolism in 5, mesenterial infarction, cerebral bleeding, brain infarction, cardiac insufficiency and third-degree burn in one patient each and unknown in 4). Death from acute toxicity was more

frequent on HDMTX plus ifosfamide than on HDMTX alone (64.7% vs. 34.7% of deaths) whereas death from tumor progression was more frequent on HDMTX alone (42.9 vs. 17.6% of deaths). Mortality from all reasons was higher in patients $\geq$ 60 years (56/337, 16.6%) than in younger patients (10/189, 5.3%) ($p<0.001$). Table 2 summarizes grade 3-4 hematologic and non-hematologic toxicities during HDMTX-based chemotherapy. Web-Table 3 (Webappendix) shows that grade 3-4 hematological toxicity was increased with HDMTX plus ifosfamide compared with HDMTX alone.

Response

The response rates to HDMTX-based chemotherapy are shown in Table 2, those for HDMTX alone compared with HDMTX/ifosfamide in Web-Table 4 (Webappendix). Central neuroradiology review was obtained for the response to HDMTX-based chemotherapy in 285 patients. A divergent assessment was provided in 28 patients (9.8%): PR→CR 22 patients, CR→PR 1 patient, PR→PD 3 patients, PD→CR 1 patient, SD→PR 1 patient. Central radiological review was performed retrospectively and thus had no impact on the treatment decision which was made in the centers according to the local radiologic evaluation unless specific advice from the trial centers in Berlin and Tübingen was sought. According to local review, 98 patients randomised to chemotherapy plus WBRT and 112 patients randomised to chemotherapy alone failed to achieve a CR with HDMTX-based primary chemotherapy. In the post-HDMTX phase of the trial, 59 of 131 patients (45%) achieved a CR with WBRT and 17 of 68 patients (25%) with HD-Ara-C.

Survival

The median follow-up was 31.8 months (range 1-104.7 months) both for the population of patients who met the eligibility criteria and received HDMTX-based chemotherapy (n=526) and for the PP population. For the PP population the median PFS in the chemotherapy+WBRT arms (A1+B1, n=154, 113 events) was 18.3 months (95% CI 11.6-25) *versus* 11.9 months (95% CI 7.3-16.5) in the chemotherapy alone arms (A2+B2, n=164, 124 events) (p=0.14, HR 0.82, 95% CI 0.64-1.07) (Figure 3A). The corresponding 2-year PFS rates were 44% and 31% (standard errors 0.04 and 0.038). The median OS was 32.4 months (95% CI 25.8-39) *versus* 37.1 months (95% CI 27.5-46.7) (p=0.7, HR 1.06, 95%CI 0.8-1.4, 97 events in 154 patients *versus* 96 events in 164 patients) (Figure 4A). Thus the primary hypothesis was not proven according to the study protocol since the lower confidence limit was smaller than 0.9. For comparison, the corresponding PFS and OS data for the ITT population are provided in Figures 3 and 4 B,D,F. Sensitivity analyses revealed that these results did not differ between the PP and the ITT populations. This was true also after stratification for initial tumor response, that is, separate analyses for patients with and without initial CR.

For patients achieving CR with HDMTX-based chemotherapy, the median PFS in arm A1 (with WBRT, n=56) was 36.3 months *versus* 21.5 months in arm A2 (no WBRT, n=96) (p=0.038), and the median OS was 38.8 months *versus* 39.4 months (p=0.56) (Figure 3C and 4C). For patients responding to HDMTX-based chemotherapy with PR, SD or PD, the median PFS in arm B1 (WBRT, n=98) was 5.6 months *versus* 3.0 months in arm B2 (HD-Ara-C, n=68) (p=0.003), and the median OS was 24.3 months *versus* 18.6 months (p=0.10) (Figure 3E and 4E). No

significant differences were found for either PFS or OS when patients treated with HDMTX were compared to those treated with HDMTX plus ifosfamide (data not shown). The median OS for all 526 patients who fulfilled the eligibility criteria was 21.5 months (95% CI: 17.8-25.1).

Prognostic factors

Univariately, only KPS and age were prognostic for OS. The median OS for patients < 60 years was 41.7 months, compared with 24.1 months in patients $\geq$ 60 years ($p<0.001$). On multivariate analysis, these both variables, and additionally gender, were significant and thus independent risk factors. In the analysis of PFS, KPS and gender, but not age, were prognostic. Note that adjustment for these factors did not change the treatment effects (Table 3). The MSK prognosis score[27], which separates patients in three prognostic groups ($\leq$ 50 years, > 50 years and KPS $\geq$ 70, > 50 years and KPS < 70) was significantly associated with PFS and OS in all patient populations (all, PP, ITT, ITT-minus-PP). In the PP population, the median PFS in the three groups was 25.07, 15.01 and 9.79 months (HR 1.34, 95% CI 1.11-1.62) and median OS was 50.69, 32.5 and 19.06 months (HR 1.56, 95% CI 1.26-1.92).

Neurotoxicity

Neurotoxicity analyses were limited to CR patients treated per protocol who remained in CR $\geq$ 3 months after completion of therapy because tumor and treatment effects on neurological function cannot be distinguished in patients with active tumor. Moreover, patients with cognitive impairment or cerebellar dysfunction

present at study entry and persisting after study treatment were excluded. Data of 79 patients, 45 in the radiotherapy arm (median age: 62) and 34 in the chemotherapy alone arm (median age: 63), were available for evaluation of clinically defined treatment-related neurotoxicity (median follow-up 49.2 months, range 37.8 – 60.5 months). Of these 79 patients, 53 had achieved CR with HDMTX-based chemotherapy alone, 22 with HDMTX-based chemotherapy plus WBRT, and 4 with HDMTX-based chemotherapy followed by HD-Ara-C. Clinically defined neurotoxicity was found in 22 patients (48.9%) in the WBRT arm and in 9 (26.5%) in the non-WBRT arms (p=0.054) after a median time of 1.7 and 2.7 years. Delayed neurotoxicity on MRI or CT was evaluated in 84 patients (median follow up: 51.4 months, range 39.8 – 63.1 months) and found in 35 of 49 (71.4%) patients in the WBRT arms and in 16 of 35 (45.7%) in the non-WBRT arms (p=0.04). Of these 84 patients, 56 had achieved CR with HDMTX-based chemotherapy alone, 25 with HDMTX-based chemotherapy plus WBRT, and 3 with HDMTX-based chemotherapy followed by HD-Ara-C.

Discussion

PCNSL has remained a major challenge in Neuro-Oncology for decades. Among the unresolved questions are the cell of origin, the lymphoma cell tropism for the brain, the low and late incidence of systemic relapse, the peculiar pattern of early response and relapse after exposure to steroids or radiotherapy, and the high risk of neurocognitive treatment sequelae.

The present randomised phase III trial of the German PCNSL Study Group (G-PCNSL-SG) sought to demonstrate that primary HDMTX-based chemotherapy alone is not inferior to primary chemotherapy followed by WBRT in the management of newly diagnosed PCNSL. With 75 active institutions, including primary care hospitals, our trial reflects the reality of PCNSL management better than oligocentric phase II trials where patients are much more selected. Centralized care in highly specialized centers may have a positive impact on outcome in PCNSL[28] , although this was not confirmed in this trial (Webappendix, Section 2). With a median age of 63 years, 131 of 551 (24%) of patients >70 years, and 65 patients (14.5%) with KPS $\leq$ 40%, there was some negative patient selection, which may explain the relatively high mortality rate on therapy and the inferior long-term outcome compared to oligocentric phase II trials with a more positively selected patient population. G-PCNSL-SG-1 is only the third randomised, the second completed, and by far the largest trial ever performed in that disease entity. The first randomised phase II trial sought to compare WBRT followed by CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone) with WBRT alone, but was closed for poor accrual,[29] the second showed superior remission rates of HDMTX plus HD-Ara-C compared with HDMTX alone.[19] In the present study, the primary hypothesis of non-inferiority of HDMTX-based chemotherapy alone compared with chemotherapy followed by WBRT according to the study protocol asking for a lower confidence limit less than 0.9 was not proven. However, the lower confidence limit was within the widely accepted non-inferiority range on 0.8, and no significant difference in OS between the study arms was found. Thus, the omission of WBRT from the primary treatment may not compromise survival, neither in patients achieving a CR with

HDMTX-based chemotherapy alone nor in those who do not and require alternative treatments early in the disease course (Figures 3 and 4). A previous retrospective analysis of heterogenously treated patients did not find a survival benefit for WBRT in addition to primary chemotherapy either.[21] For patients achieving a CR with chemotherapy alone, reducing the WBRT dose was reported to compromise survival in a small phase II study.[30] Yet, others felt that the dose of WBRT can be safely reduced in patients achieving CR with primary HDMTX-based immunochemotherapy.[31] Here, WBRT provided a gain in PFS that may be clinically relevant in patients who do not experience relevant toxicity from WBRT (Figure 3). Moreover, WBRT was more effective in patients failing to achieve a CR in response to HDMTX-based chemotherapy than HD-Ara-C, confirming the importance of WBRT for disease control.[32] This did not translate into a survival benefit, most probably because of the efficacy of other treatments administered at relapse rather than enhanced mortality from WBRT.

Current efforts to improve outcome in PCNSL explore various options, including (1) HDMTX-based polychemotherapy with intrathecal chemotherapy,[33-35] (2) HDMTX-based polychemotherapy plus blood-brain barrier disruption[36] and (3) HDMTX-based polychemotherapy followed by autologous stem cell transplantation with or without adjuvant radiotherapy.[37-38] A more puristic approach would try to improve on the results obtained with HDMTX alone by combining HDMTX with another chemotherapeutic drug instead of WBRT, e.g., with HD-Ara-C[19] or with ifosfamide as done here. Although higher response rates can be obtained with drug combinations, it remains uncertain whether this benefit translates into prolonged disease control and survival. While the efficacy of chemotherapy in our trial was lower than that of

polychemotherapy in some phase II trials,[33,37] it remains to be demonstrated that polychemotherapy is superior to HDMTX alone in a less selected patient population such as the G-PCNSL-SG-1 PP population. In the present study, CR was significantly associated with prolonged OS, as previously observed.[28] The median OS was 39 months in CR patients *versus* 22 months in non-CR patients in the ITT population ($p < 0.001$). However, the addition of any cytotoxic agent to HDMTX will invariably increase toxicity as observed here for ifosfamide (Web-Table 3, Webappendix) or previously for HD-Ara-C.[19]

The study has several limitations which are partially explained by insufficient funding. The upfront randomisation had historical reasons. It was introduced based on the experience of a prior study[28] in which patients with CR after primary chemotherapy often declined to be randomised to WBRT. This might have introduced imbalances between arms. However, there were no significant differences in age and KPS in the two study arms in the PP population. Moreover, no significant differences in OS according to treatment arm were found when all patients (n=551), all patients meeting the inclusion criteria (n=526), or the ITT-minus-PP populations (n=93) were analyzed (data not shown), indicating that the outcome in the two study arms in the PP population was not biased by patient selection. Further, we do not dismiss the flaw of 60% power from the statistical point of view. However, the framework of the clinical setting of PCNSL in the nineties needs to be considered. There were very few international studies in the brain tumor field at all and it took until 2009 (!) that the first (small) randomised trial in PCNSL was concluded and published (19). There is no doubt that we would not plan this trial today in a similar way as we did 12 years ago. The frequent protocol violations (ITT

patients, n=411 minus PP patients, n=318: n=93), the high rate of patients lost to follow-up (10%), the publication of preliminary data from the trial,[22-26] and the (retrospectively unnecessary) protocol amendment introducing ifosfamide represent further limitations. The neurotoxicity analysis suffers from the small sample size and selection cannot be ruled out.

Age and KPS were confirmed as the most important treatment-independent risk factors for OS. Although response rates were comparable in patients < versus ≥ 60 years of age, PFS and OS were inferior in elder patients. Considering the much higher toxicity in this population, future studies must focus on reducing toxicity while maintaining remission. For younger patients a curative approach, including the evaluation of HD chemotherapy with stem cell transplantation, remains the prime goal. Although WBRT plays a role in disease control, the lack of a survival benefit observed here may justify its omission from first-line treatment in PCNSL.

Research in context

Systematic review. A formal systematic review was not performed when designing the clinical trial. At the end of the 90ies, data on the therapy of PCNSL was scarce with some retrospective analyses and only a few small prospective single arm trials. These were systematically reanalysed and reevaluated as summarized in the introduction of the G-PCNSL-SG-1 study protocol (www.neuroonkologie.de/index.php?id=58) which is only available in German language. Single-arm phase II studies had indicated that long-term disease control can be achieved by applying WBRT after HDMTX-based chemotherapy, however, with a high risk of late neurotoxicity, particularly in the elderly. In the first trials using chemotherapy alone and postponing WBRT until progression, a

similarly long-term control with less late neurotoxicity was suggested. Thus, it appeared appropriate to evaluate the role of WBRT in the primary therapy of PCNSL regarding both long-term disease control and late neurotoxicity.

Interpretation. We can no longer recommend the use of WBRT as a standard of care for newly diagnosed PCNSL. Clinicians should enrol patients into clinical trials whenever possible. Outside clinical trials, clinicians have to weigh the PFS benefit afforded by WBRT against the late neurotoxicity of WBRT.

Contributors

ET, AK, LK, UH, MB and MW designed and wrote the study protocol. ET, AK, LK, FG, MR, AR, BH, TT, TH, ML, TB, LF, KJ, UH, MB and MW contributed patients to the trial. PM performed the statistical analyses. TN was responsible for reference neuroradiology. TP was responsible for reference neuropathology. LP and MB were responsible for reference radiation oncology. ET, AK, PM and MW wrote the manuscript. All authors approved the manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

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Table 1. Patient characteristics.

	PP **N=318 (%)**	**ITT minus PP** **N=93 (%)**
Demographics		
Age (years)		
Median	61	63
Range	19-84	31-79
< 60	140 (44)	30 (32.3)
≥ 60	178 (56)	63 (67.7)
Sex		
Male	183 (57.5)	53 (57)
Female	135 (42.5)	40 (43)
Diagnostic procedure		
Surgery		
Gross total resection	45 (14.2)	10 (10.8)
Partial resection	52 (16.4)	6 (6.5)
Open biopsy	32 (10.1)	8 (8.6)
Stereotactic biopsy	184 (57.8)	68 (73.1)
CSF cytology	3 (0.9)	1 (1.1)
Vitreal cytology	2 (0.6)	0
Neuropathological diagnosis		
Diffuse large cell B cell lymphoma	273 (85.8)	82 (88.2)

T-NHL	12 (3.8)	1 (1.1)
Other B-NHL	10 (3.1)	4 (4.3)
No specification	23 (7.2)	6 (6.5)
Neuroimaging on diagnosis		
MRI	264 (83)	75 (80.6)
CT	53 (16.7)	15 (16.1)
No specification	1 (0.3)	3 (3.2)
LDH		
Normal	128 (40.3)	34 (36.6)
Elevated	58 (18.2)	23 (24.7)
Not done	17 (5.3)	9 (9.7)
No specification	115 (36.2)	27 (29.0)
Karnofsky Performance Score		
Median/Range	80.0 (30-100)	80.0 (30-100)
CSF studies / Slit lamp examination		
Lymphoma cells in the CSF		
No	158 (49.7)	39 (41.9)
Yes	26 (8.2)	11 (11.8)
Suspect	9 (2.8)	1 (1.1)
No specification	125 (39.3)	42 (45.2)
CSF protein		
$\leq$ 60 mg/dl	93 (29.3)	26 (28.0)
> 60 mg/dl	91 (28.6)	25 (26.9)

No specification	134 (42.1)	42 (45.1)
Slit lamp examination		
No	118 (37.1)	23 (24.7)
Yes	177 (55.7)	58 (62.4)
No specification	23 (7.2)	12 (12.9)
Ocular involvement on slit lamp		
No	165 (51.9)	53 (57.0)
Yes	9 (2.8)	3 (3.2)
No specification	144 (45.3)	37 (39.8)

Table 2. Response by local assessment and WHO Grade 3-4 toxicity of primary HDMTX-based chemotherapy by age.[1]

	All patients n=526	< 60 yrs N=189	≥ 60 yrs n=337
Response (n, %)			
CR	182 (34.6)	72 (38.1)	110 (32.6)
PR	101 (19.2)	48 (25.4)	53 (15.7)
SD	24 (4.6)	6 (3.2)	18 (5.3)
PD	123 (23.4)	48 (25.4)	75 (22.3)
Died on therapy	66 (12.5)	10 (5.3)	56 (16.6)
Unknown	30 (5.7)	5 (2.6)	25 (7.4)
Hematologic toxicity (n, %)[1]			
Leukopenia, n=470	112 (23.8)	23 (13.9)	89 (29.3)
Infections, n=475	128 (26.9)	29 (17.7)	99 (31.8)
Anemia, n=469	65 (13.8)	14 (8.4)	51 (16.8)
Thrombocytopenia, n=470	54 (11.5)	8 (4.8)	46 (15.1)
Non-hematologic toxicity (n, %)[1]			
Transaminase elevation, n=458	85 (18.6)	35 (21.6)	50 (16.9)
Lung toxicity, n=460	45 (9.8)	10 (6.1)	35 (11.8)
Stomatitis, n=459	22 (4.8)	3 (1.8)	19 (6.4)

Urea/creatinine elevation, n=470	17 (3.6)	4 (2.4)	13 (4.3)
Impaired consciousness, n=457	36 (7.9)	9 (5.6)	27 (9.1)
Peripheral neuropathy, n=451	18 (4,0)	3 (1.9)	15 (5.2)
Vomiting, n=461	10 (2.2)	4 (2.5)	6 (2.0)

[1]Data provided for (and relative to) all patients with data on toxicity available.

Table 3. Univariate and multivariate analyses for PFS and OS.

Covariate	Univariate analysis (Simple Cox regression model)			Multivariate analysis (Multiple Cox regression model *without* variable selection)		
	HR	P value	95% CI	HR	P value	95% CI
	PFS					
Age[1]	1.22	0.13	0.95-1.59	1.11	0.46	0.84-1.49
KPS[2]	1.09	0.02	1.01-1.18	1.11	0.012	1.02-1.20
Gender[3]	0.84	0.19	0.65-1.09	0.73	0.037	0.55-0.98
Study arm[4]	0.82	0.14	0.64-1.07	0.82	0.18	0.62-1.09
HDMTX/Ifo[5]	0.94	0.74	0.66-1.34	0.82	0.33	0.55-1.22
	OS					
Age[1]	1.69	< 0.001	1.26-2.26	1.54	0.008	1.12-2.12
KPS[2]	1.16	<0.001	1.07-1.26	1.16	0.001	1.07-1.27
Gender[3]	0.82	0.17	0.61-1.09	0.70	0.031	0.51-0.97
Study arm[4]	1.06	0.71	0.80-1.40	1.05	0.74	0.77-1.44
HDMTX/Ifo[5]	1.05	0.84	0.66-1.65	1.11	0.69	0.68-1.81

[1] HR refers to patients ≥ 60 *versus* patients < 60 years of age
[2] HR refers to 10% *decrease* of KPS
[3] HR refers to female *versus* male patients
[4] HR refers to WBRT versus non WBRT
[5] HR ratio refers to HDMTX plus ifosfamide *versus* HDMTX alone

Figure legends

Figure 1. G-PCNSL-SG-1 trial design.

Figure 2. CONSORT chart.

Figure 3. PFS in the PP and ITT populations by treatment arm: A, all PP patients, B, all ITT patients; C, A1 (CR, plus WBRT) *versus* A2 (CR, no WBRT), PP population, D, ITT population; E, B1 (CR, plus WBRT) *versus* B2 (CR, no WBRT), PP population, F, ITT population.

Figure 4. OS in the PP and ITT populations by treatment arm: A, all PP patients, B, all ITT patients; C, A1 (CR, plus WBRT) *versus* A2 (CR, no WBRT), PP population, D, ITT population ; E, B1 (CR, plus WBRT) *versus* B2 (CR, no WBRT), PP population, F, ITT population.

Webappendix

Section 1

The following centers and investigators participated in the trial by enrolling the indicated numbers of patients: Berlin, Charité (Drs. Kiewe, Mannsmann, Sternemann, Vajkoczy, n=66), Tübingen (Drs. Brugger, Herrlinger, Küker, Meyermann, Möhle, n=35), Oldenburg (Drs. Klasen, Steder, Temmesfeld, n=34), Bielefeld Gilead (Drs. Krümpelmann, Rohden, Tagliazadeh, Weißinger, n=33), Essen (Drs. Dührsen, Fauser, Meusers, Nowrousian, Rauhut, Sack, Seeber, n=33), Bremen (Drs. Kaun, Thomssen, n=27), Magdeburg (Drs. Fischer, Königsmann, Markmann, Ochel, Pleger, n=20), Mainz (Drs. Huber, Nguyen-Huu, Wölfel, n=20), Rostock (Drs. Freund, Lück, n=16), Munich LMU (Drs. Dudel, Straube, n=16), Trier (Drs. Kirchen, Kölbel, Ley, Weber, n=15), Stuttgart KH (Drs. Assmann, Schleicher, n=13), Minden (Drs. Busse, Haukamp, Schubert, n=11), Münster (Drs. Berdel, Kerkhoff, Liersch, Meesters, Stelljes, n=11), Nürnberg (Drs. Birkmann, Frank, Hofmann, n=11), Dessau (Drs. Florschütz, Kellner, Schön, Schwalbe, n=10), Hamburg North (Drs. Aydogan, Wallat, Waschewski, n=8), Hildesheim (Drs. Adomeit, Kaiser, n=8), Hamm (Drs. Costantino, Dürk, Hilleke, Melzner, Pelz, n=8), Karlsruhe (Drs. Fischer, Kubin, n=8), Munich TU (Drs. Peschel, von Bubnoff, n=8), Lübeck (Drs. Fehm, Heide, Niehoff, Wagner, n=7), Mannheim (Drs. Hehlmann, König, La Rosee, Lengfelder, n=7), Stuttgart BH (Drs. Hoffmann, n=7), Bamberg (Drs. Hupp, Krauseneck, Thiel, Weber, n=7), Hannover (Drs. Dengler, Ganser, Heidenreich, Kofahl-Krause, Peest, Tatagiba, n=6), Homburg (Drs. Held, Ketter, Murawski, Pfreundschuh, Steudel, n=6), Saalfeld (Drs. Fenchel, Meeier, n=5), Regensburg BB (Drs. Baumgart, Kreuser, Moribundi, Stauder, n=5), Cottbus (Drs. Peter, Rudoph, n=4), Bremerhaven (Drs. Ahrens, Kurtz, Schmeck, n=4), Düsseldorf (Drs. Gattermann, Germing, Pape, Schmidt, n=4), Bochum KK (Drs. Engelhard, Haders, n=4), Stuttgart MH (Drs. Denzlinger, Walther, Wedekind, Schmid, n=4), Regensburg UK (Drs. Andreesen, Blank, Bogdahn, Hau, Herbst, Krause, Moriabadi, n=4), Neubrandenburg (Drs. Bonhoeffer, Grobe, n=3), Göttingen (Drs. Hess, Jung, Lehmann, Schmidberger, Strik, Trümper, n=3), Siegen Ev. Jung-Stilling (Dr. Klump, n=3), Hagen (Drs. Eimermacher, Haak, Lindemann, von Rethwisch, n=3), Frankfurt UK (Drs. Chow, Hölzer, n=3), Kaiserslautern (Drs. Hübner, Link, n=3), Villingen-Schwenningen (Drs. Brugger, Lohmann, n=3), Halle (Dr. Rainov, n=2), Berlin VM (Dr. Rühl, n=2), Berlin HH (Drs. Voigt, Zerm, n=2), Brandenburg/Havel (Dr. Deckert, n=2), Stralsund (Drs. Gerecke, Lüdtke, n=2), Kiel (Drs. Hartwig, Kneba, Mehdorn, Strege, Vieler, n=2), Celle (Drs. Holtz, Marquard, Sauerland, n=2), Marburg (Drs. Kaiser, Neubauer, Wündisch, n=2), Goch (Dr. Runde, n=2), Siegen St. Marten (Drs. Gaska, Gassmann, n=2), Stuttgart DK (Drs. Bair, Bichler, Mück, Wöhr, n=2), Leipzig (Drs. Harder, Kortmann, n=1), Jena UK (Dr. Adam, n=1), Bad Saarow (Drs. Fuss, Schultze, n=1), Hamburg Altona (Dr. Wernecke, n=1), Flensburg (Dr. Saal, n=1), Emden (Dr. Becker, n=1), Rotenburg (Drs. Haits, Reinhardt, n=1), Hameln-Pyrmont (Dr. Buhrmann, n=1), Gütersloh (Drs. Depenbusch, Gropp, Westheider, n=1), Fulda (Dr. Ulu, n=1), Aachen (Dr. Gehbauer, n=1), Koblenz (Dr. Weide, n=1), Hagen (Drs. Ansorge, Souchon, n=1), Munich-Harlaching (Dr. Hentrich, n=1), Munich-Neuperlach (Dr.Schäfer, n=1), Erlangen (Drs. Grüner, Sauer, n=1), Passau (Dr. Prügel, n=1), Würzburg (Dr. Goebeler, n=1), and various doctors in private practice (n=3).

Section 2

To analyse the outcome according to center, we divided the centers into two groups containing approximately 50% of patients each: those with a total number of $\leq$ 20 or >20 enrolled patients. There was no significant difference in these two patient groups concerning age and KPS. Interestingly, the OS was longer in the first group both for the PP (39.06 *versus* 31.47 months, p=0.059, HR 1.31, 95% CI 0.99-1.74) and ITT population (37.06 *versus* 31.47 months, p=0.06, HR 1.27, 95%CI 0.99-1.63) whereas no differences were found in all patients and in the ITT-minus-PP population. PFS was significantly better in "smaller centers", too: 15.67 *versus* 13.63 months, p=0.026, HR1.34, 95%CI 1.03-1.73). The CR rate was reported higher in "small centers" than in "large centers" (47.5% *versus* 41.2% (ITT) and 51.9% *versus* 43.9% (PP)) whereas total response rate, PD rate and mortality on therapy were not different. Thus, small centers did not negatively impact the outcome parameters in this trial.

Web-Table 1. Salvage treatments by study arm

Salvage treatments	Arms A1/B1 (WBRT) (n=203)	Arms A2/B2 (no WBRT) (n=208)
WBRT	n=13*	n=41
Chemotherapy	n=37 n=14 topotecan n=6 CHOP regimen (patients with systemic relapse only) n=3 temozolomide n=3 HD-Ara-C n=2 HD-BCNU/thiotepa with autologous stem cell transplantation (ASCT) n=9 other (one patient each: HDMTX, PCV, bendamustine, ifosfamide, topotecan/ifosfamide, Ara-C/etoposide, gemcitabine/oxaliplatin, MTX or liposomal Ara-C intrathecally for meningeal relapse)	n=23 n=7 topotecan n=4 HDMTX/ifosfamide n=3 HD-BCNU/thiotepa with ASCT n=2 CHOP regimen (patients with systemic relapse only) n=7 other (one patient each: ifosfamide, idarubicine/dexamethasone/etoposide/Ara-C/rituximab, temozolomide/rituximab, topotecan/BCNU, HD-Ara-C/trofosfamide, PCV, intraocular rituximab for ocular relapse)
WBRT and chemotherapy	n=12 n=2 HD-Ara-C n=2 topotecan n=8 other (one patient each: HD-Ara-C/HDMTX, temozolomide/rituximab, HDMTX/ifosfamide, procarbazine, HD-BCNU/thiotepa with ASCT, HDMTX, MTX/Ara-C intrathecally for meningeal relapse, intraocular MTX for ocular relapse)	n=33 n=6 topotecan n=6 PCV n=6 HD-BCNU/thiotepa with ASCT n=5 temozolomide n=3 CHOP regimen n=3 HDMTX/ifosfamide n=2 HD-Ara-C n=1 HD-Ara-C/thiotepa n=1 unknown

*The 25 patients treated with salvage radiotherapy had not received WBRT as randomized and were thus not irradiated twice.

Web-Table 2. Diagnoses on central neuropathology review (n=272).[1]

	n (%)
Diffuse large B cell lymphoma	241 (88.6)
CNS tissue, consistent with diffuse large B cell lymphoma	5 (1.8)
CNS tissue, probably diffuse large B cell lymphoma	7 (2.6)
CNS tissue without tumor	7 (2.6)
Other lymphomas:	
T-NHL	6 (2.2)
Anaplastic large cell lymphoma	2 (0.7)
Low-grade B-NHL	2 (0.7)
B-NHL with plasmacytoid differentiation	1 (0.4)
Anaplastic plasmacytoma, EBV-positive	1 (0.4)

[1]272 biopsy specimens were available for histopathology review. All tissue samples were analysed by conventional stainings, including hematoxylin/eosin, reticulin and Giemsa staining, as well as immunohistochemical staining for CD45, CD20, CD3, CD68, Ki-67 (antibody MIB-1) and glial fibrillary acidic protein (antibodies from Dakopatts, Hamburg, Germany). In some cases, CD138, bcl-2, bcl-6, mum-1, CD10 and CD30 antibodies were employed to further characterize individual cases of non-diffuse large B cell lymphoma. Classification of tumors followed the current revised WHO classifications for lymphomas and central nervous tumors, respectively.

Web-Table 3. WHO grade 3-4 toxicity of HDMTX compared with HDMTX plus ifosfamide.[1]

	HDMTX n=401	HDMTX/ifosfamide n=125
Hematologic (n, %)		
Neutropenia, n=470	43 (11.8)	69 (64.5)
Infection, n=475	80 (21.9)	48 (44)
Anemia, n=469	41 (11.3)	24 (22.6)
Thrombocytopenia, n=470	34 (9.4)	20 (18.5)
Non-hematologic (n, %)		
Transaminase elevation, n=458	62 (17.5)	23 (22.1)
Lung toxicity, n=460	30 (8.34)	15 (14.7)
Stomatitis, n=459	17 (4.8)	5 (4.9)
Urea/creatinine elevation, n=470	14 (3.9)	3 (2.8)
Impaired consciousness, n=457	26 (7.3)	10 (9.7)
Peripheral neuropathy, n=451	15 (4.3)	3 (3.0)
Vomiting, n=461	7 (2.0)	3 (2.9)

[1]Data provided for (and relative to) all patients with data on toxicity available.

Web-Table 4. Response to HDMTX *versus* HDMTX plus ifosfamide by age (n=526).

	CR (%)	PR (%)	SD (%)	PD (%)	Died (%)	Unknown (%)
HDMTX All, n=401	130 (32.4)	71 (17.7)	21 (5.2)	104 (25.9)	49 (12.2)	26 (6.5)
<60, n=149	56 (37.6)	34 (22.8)	5 (3.4)	42 (28.2)	7 (4.7)	5 (3.4)
≥60, n=252	74 (29.4)	37 (14.7)	16 (6.3)	62 (24.6)	42 (16.7)	21 (8.3)
HDMTX/ifosfamide All, n=125	52 (41.6)	30 (24.0)	3 (2.4)	19 (15.2)	17 (13.6)	4 (3.2)
<60, n=40	16 (40)	14 (35)	1 (2.5)	6 (15)	3 (7.5)	0
≥60, n=85	36 (42.4)	16 (18.8)	2 (2.4)	13 (15.3)	14 (16.5)	4 (4.7)

Figure 1. G-PCNSL-SG-1 trial design

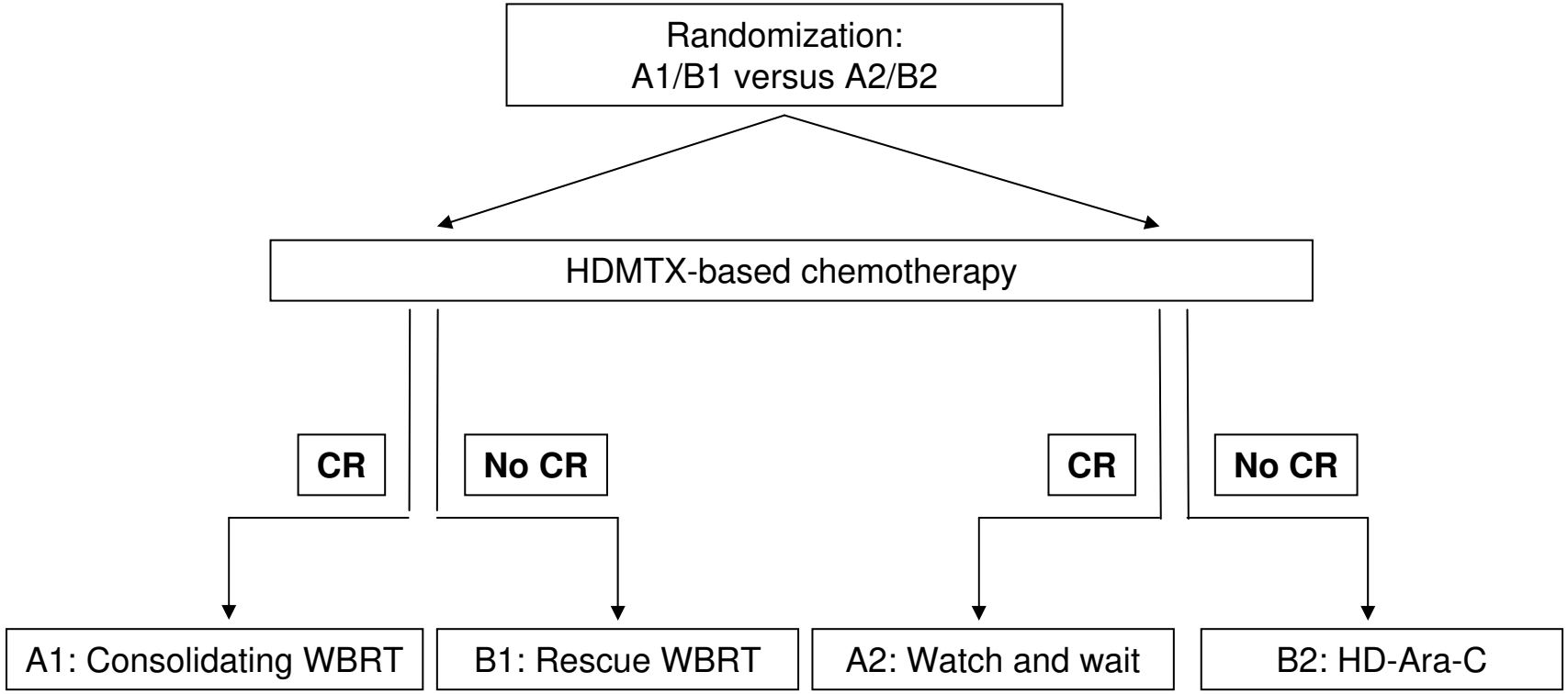
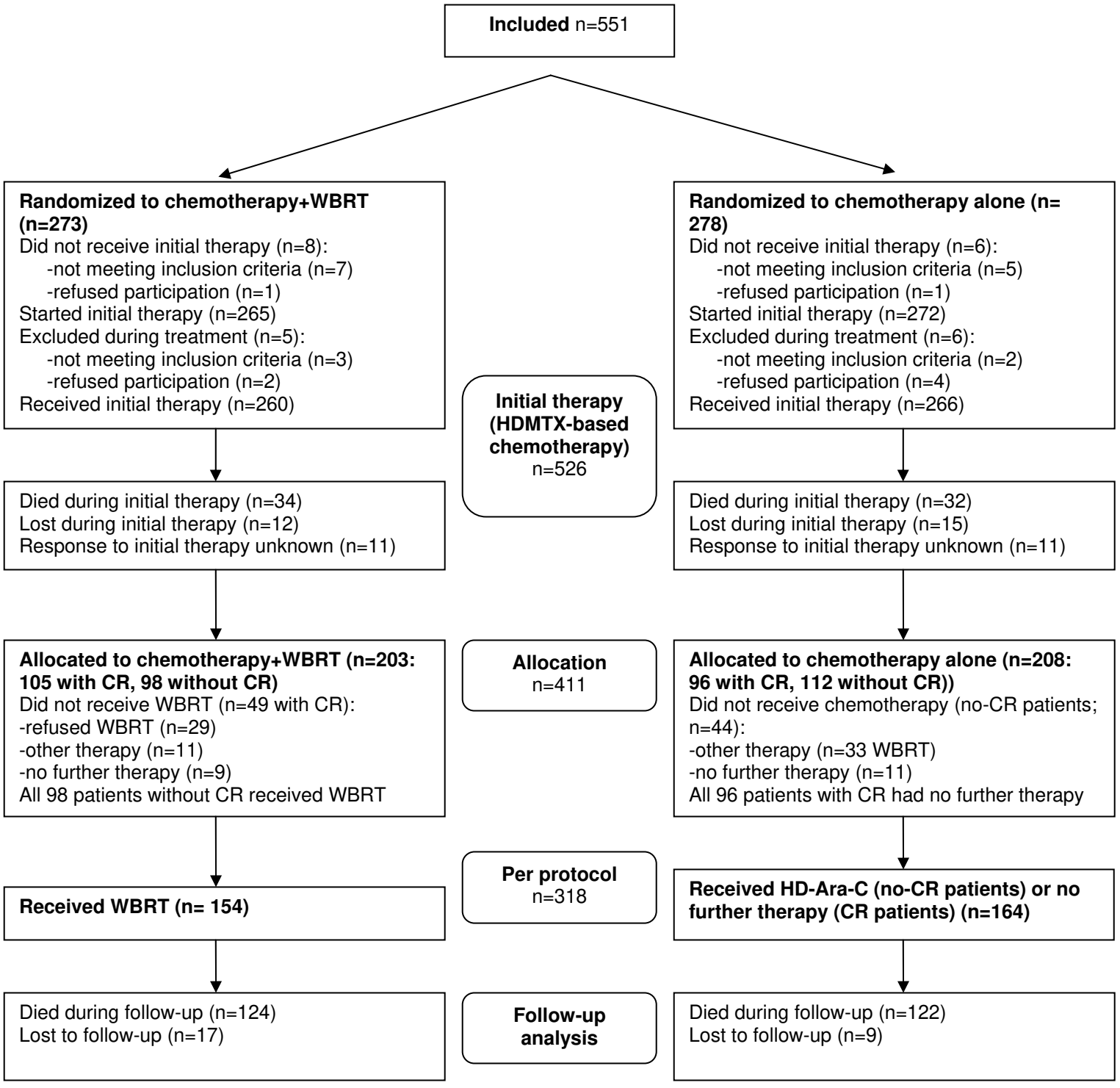
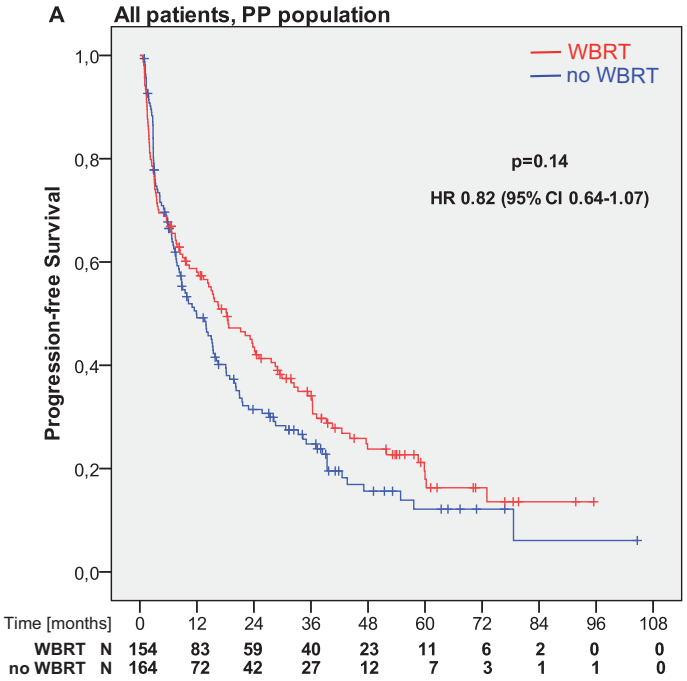
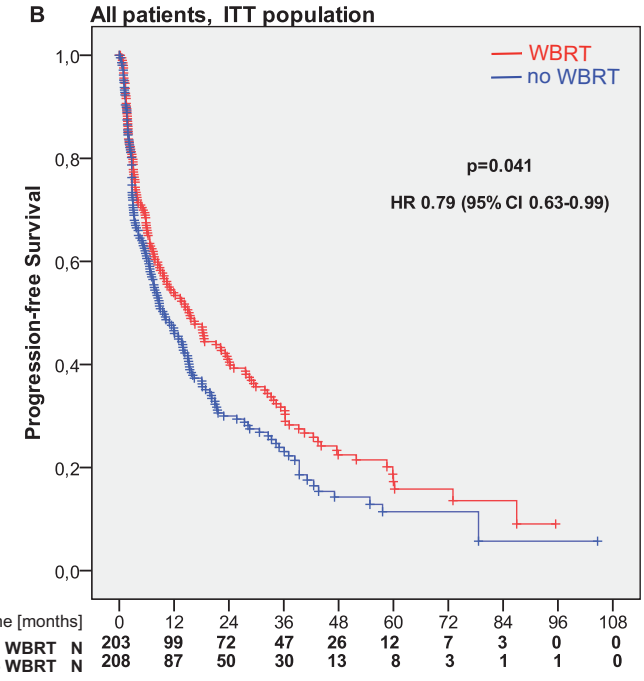


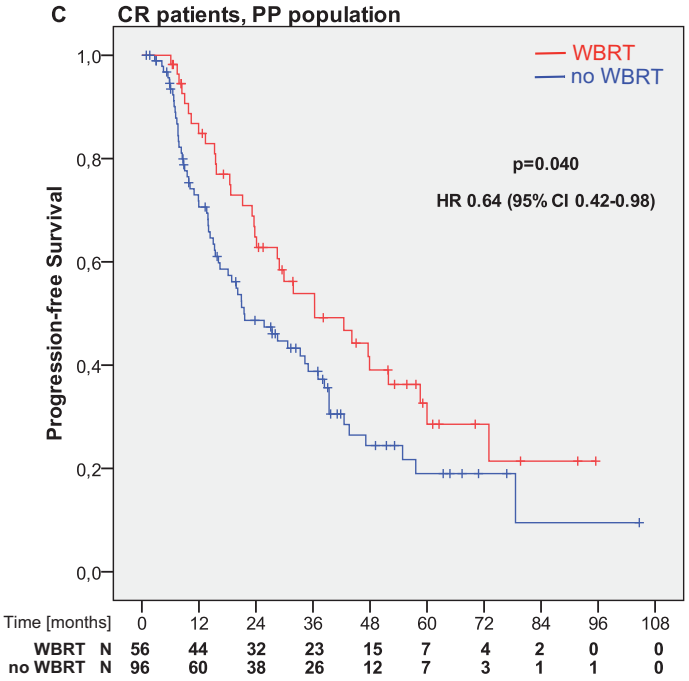
Figure 2. Modified CONSORT flowchart

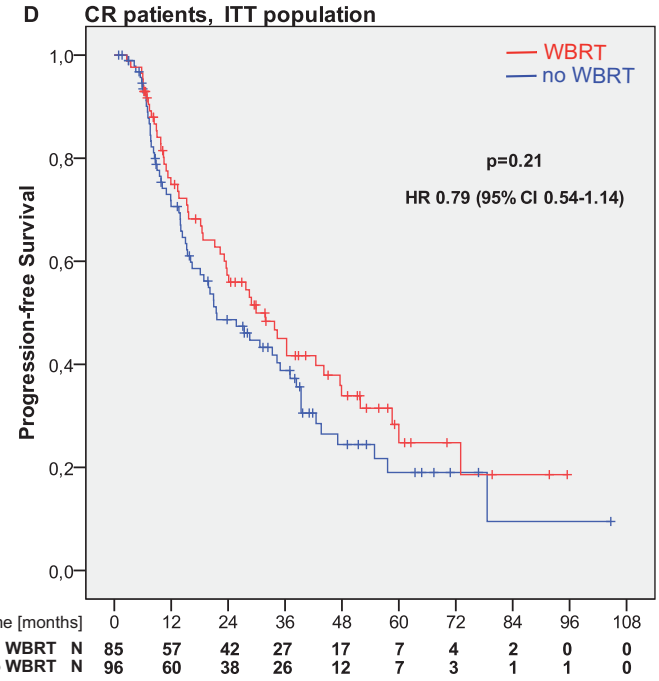


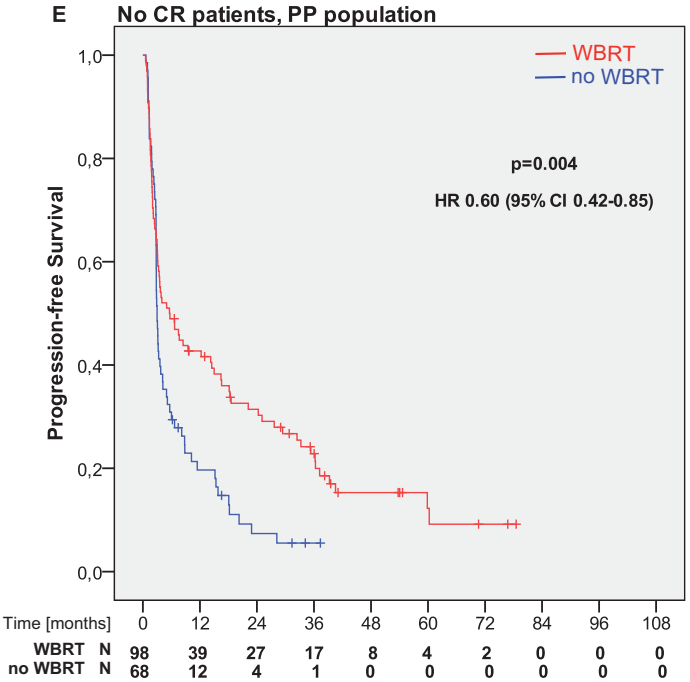
1 none of those without CR did not receive WBRT in the chemo+WBRT group
2

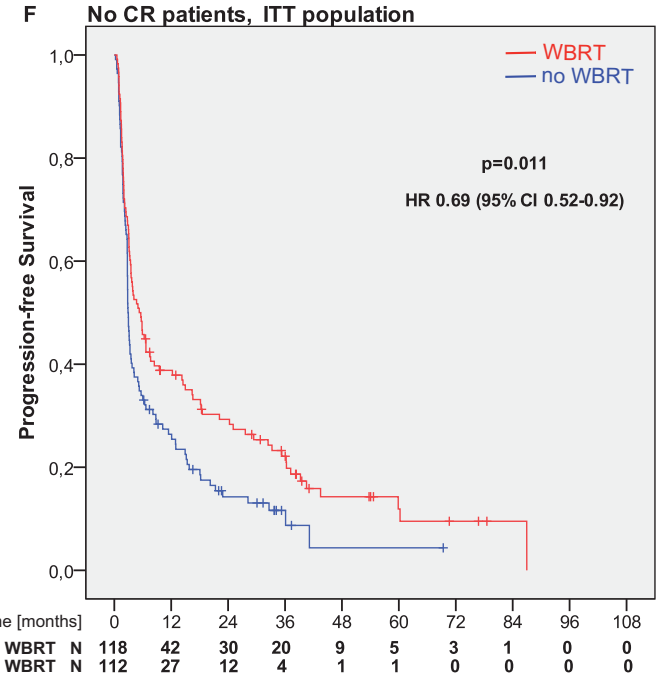

A
All patients, PP population
WBRT
no WBRT
p=0.14
HR 0.82 (95% CI 0.64-1.07)
Progression-free Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 154 83 59 40 23 11 6 2 0 0
no WBRT N 164 72 42 27 12 7 3 1 1 0

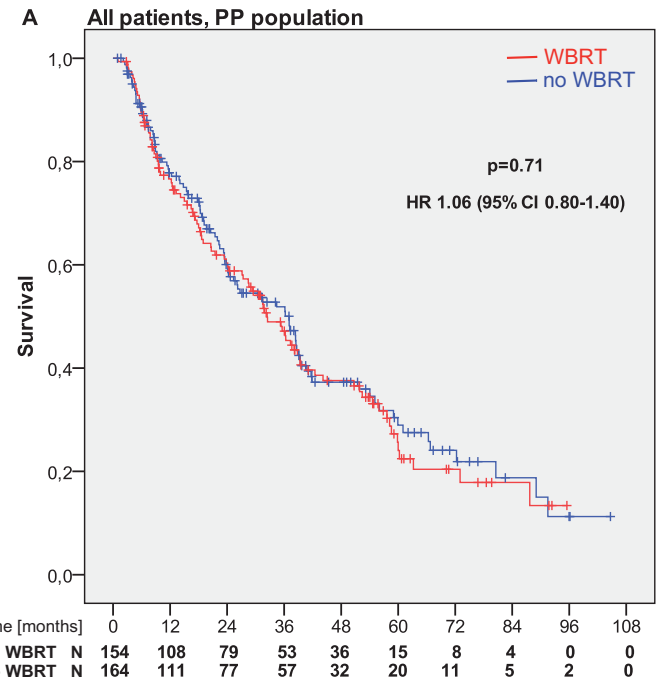

B
All patients, ITT population
WBRT
no WBRT
p=0.041
HR 0.79 (95% CI 0.63-0.99)
Progression-free Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 203 99 72 47 26 12 7 3 0 0
no WBRT N 208 87 50 30 13 8 3 1 1 0

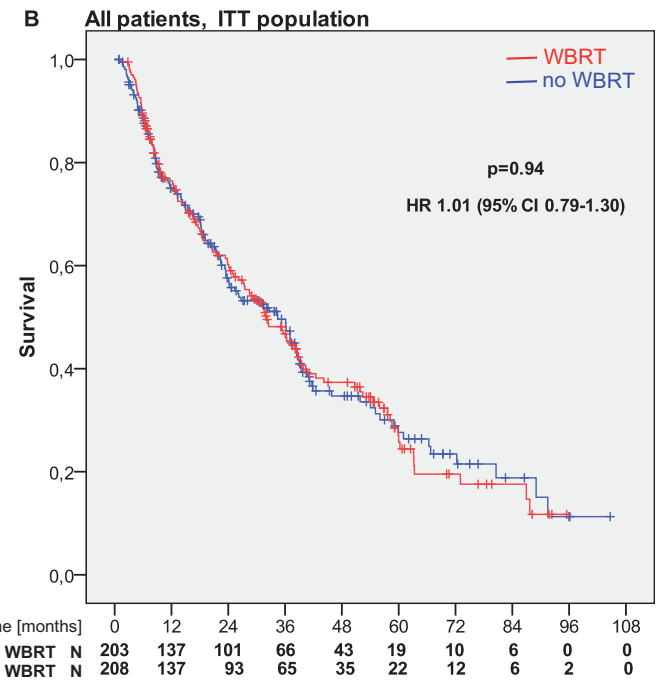

C
CR patients, PP population
WBRT
no WBRT
p=0.040
HR 0.64 (95% CI 0.42-0.98)
Progression-free Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 56 44 32 23 15 7 4 2 0 0
no WBRT N 96 60 38 26 12 7 3 1 1 0

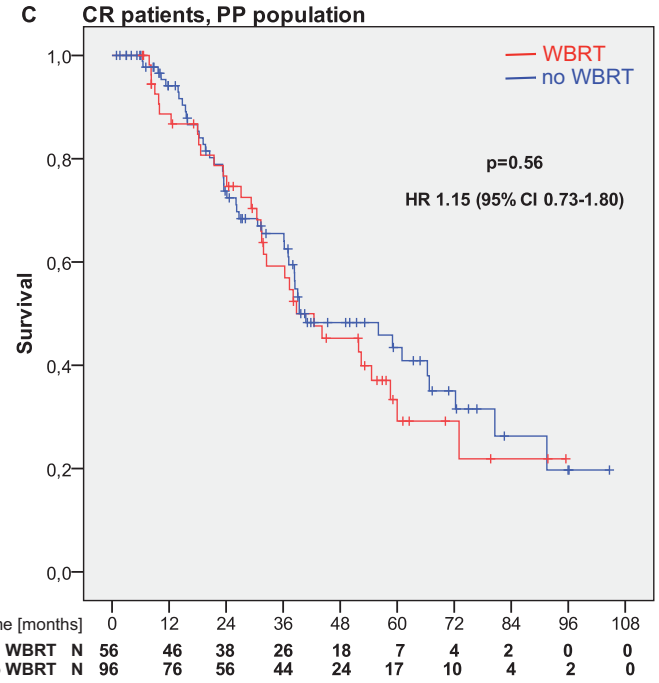

D
CR patients, ITT population
WBRT
no WBRT
p=0.21
HR 0.79 (95% CI 0.54-1.14)
Progression-free Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 85 57 42 27 17 7 4 2 0 0
no WBRT N 96 60 38 26 12 7 3 1 1 0

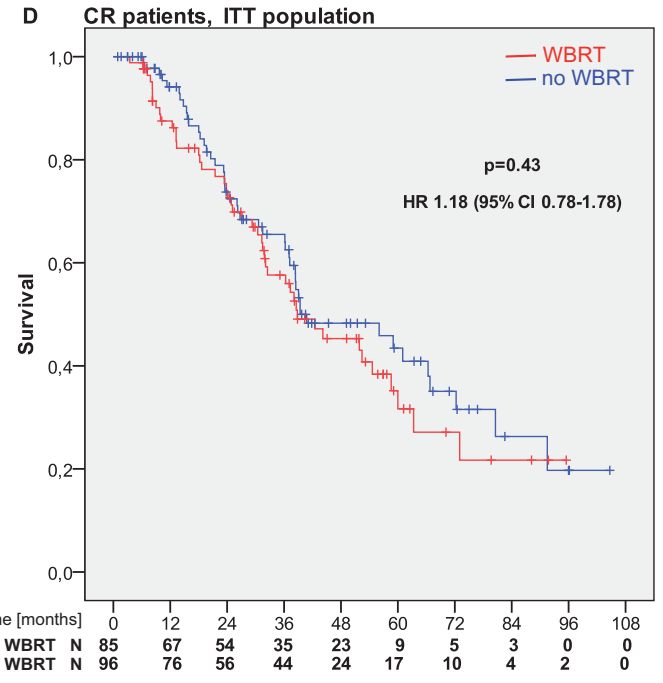

E
No CR patients, PP population
WBRT
no WBRT
p=0.004
HR 0.60 (95% CI 0.42-0.85)
Progression-free Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 98 39 27 17 8 4 2 0 0 0
no WBRT N 68 12 4 1 0 0 0 0 0 0

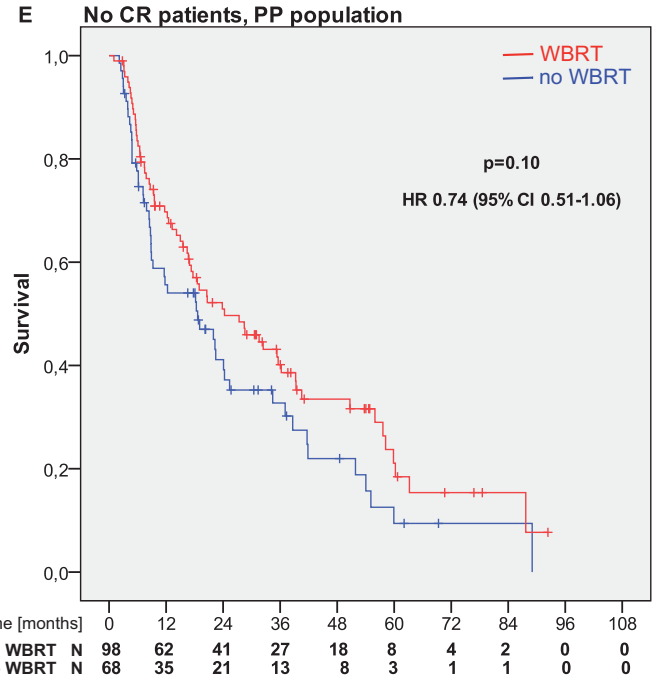

F
No CR patients, ITT population
WBRT
no WBRT
p=0.011
HR 0.69 (95% CI 0.52-0.92)
Progression-free Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 118 42 30 20 9 5 3 1 0 0
no WBRT N 112 27 12 4 1 1 0 0 0 0

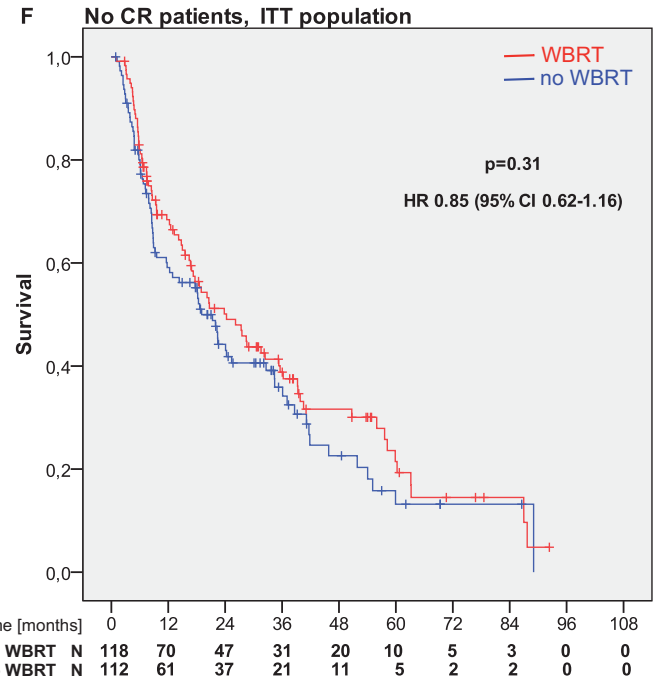

A
All patients, PP population
WBRT
no WBRT
p=0.71
HR 1.06 (95% CI 0.80-1.40)
Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 154 108 79 53 36 15 8 4 0 0
no WBRT N 164 111 77 57 32 20 11 5 2 0


B
All patients, ITT population
WBRT
no WBRT
p=0.94
HR 1.01 (95% CI 0.79-1.30)
Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 203 137 101 66 43 19 10 6 0 0
no WBRT N 208 137 93 65 35 22 12 6 2 0


C
CR patients, PP population
WBRT
no WBRT
p=0.56
HR 1.15 (95% CI 0.73-1.80)
Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 56 46 38 26 18 7 4 2 0 0
no WBRT N 96 76 56 44 24 17 10 4 2 0


D
CR patients, ITT population
WBRT
no WBRT
p=0.43
HR 1.18 (95% CI 0.78-1.78)
Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 85 67 54 35 23 9 5 3 0 0
no WBRT N 96 76 56 44 24 17 10 4 2 0


E
No CR patients, PP population
WBRT
no WBRT
p=0.10
HR 0.74 (95% CI 0.51-1.06)
Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 98 62 41 27 18 8 4 2 0 0
no WBRT N 68 35 21 13 8 3 1 1 0 0


F
No CR patients, ITT population
WBRT
no WBRT
p=0.31
HR 0.85 (95% CI 0.62-1.16)
Survival
1,0
0,8
0,6
0,4
0,2
0,0
Time [months] 0 12 24 36 48 60 72 84 96 108
WBRT N 118 70 47 31 20 10 5 3 0 0
no WBRT N 112 61 37 21 11 5 2 2 0 0